ABSTRACT

Arthritis causes considerable patient morbidity and substantial health care resource utilization. One important contributing component to the overall cost burden of this condition is the variety of expenditures attributable to the adverse effects of arthritis therapy. Nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) are a mainstay of medical treatment for patients with arthritis because of their well-established anti-inflammatory and analgesic effects. Generally well tolerated, traditional NSAIDs nevertheless cause adverse gastrointestinal (GI) effects in a proportion of patients. Because nonselective NSAIDs are so widely used, these GI adverse events cause significant morbidity and mortality, accounting for substantial additional health care expenditures. Data from controlled investigations document the enhanced GI safety of cyclooxygenase (COX)-2–selective inhibitors, or coxibs, when compared with nonselective NSAIDs. As a result of this improved safety profile, patients treated with coxibs use significantly fewer GI-related health care resources (eg, medications, procedures) than patients treated with nonselective NSAIDs. Thus, available clinical and economic data suggest that the use of coxibs has the potential to result in important clinical GI benefits at an acceptable incremental cost for all chronic NSAID users. For individuals who are at an increased risk of developing GI complications attributable to NSAIDs, coxibs are clearly a cost-effective treatment option.

More than 20 million adults in the United States have arthritis, a general diagnosis used to describe joint inflammation or pain. The two most common forms of arthritis are osteoarthritis and rheumatoid arthritis. Although rarely fatal, arthritis causes considerable disability and morbidity. Yelin and Callahan used the 1990-1992 National Health Interview Survey and a literature review to estimate that health care utilization due to all musculoskeletal conditions totaled $149.4 billion. Nearly half (48%) of these expenditures were due to direct medical care costs (315 million physician visits and over 8 million hospitalizations), and the remaining amount resulted from lost wages. An updated economic burden of musculoskeletal conditions was derived using the 1996
Medical Expenditure Panel Survey, a national sample of 21,571 people, 4,161 (19%) of whom reported at least one musculoskeletal condition. An analysis of health care utilization by this cohort of patients, representing nearly 54 million Americans with at least one musculoskeletal condition, revealed that persons with musculoskeletal conditions were more likely to use every type of health care service than either persons without chronic conditions or those with other chronic conditions. Persons with musculoskeletal conditions had total medical care expenditures that were more than 50% higher than those of persons without musculoskeletal conditions—$3,578 versus $2,313. This figure extrapolates to a national total of $193 billion annually. The three largest components of care were: hospitalizations (37%), physician visits (23%), and prescription drugs (16%).

FOCUS ON PRESCRIPTION DRUGS

Prescription drugs account for approximately one-sixth of arthritis expenditures and 8% to 10% of spending for health care in the United States. Despite this relatively small share of the health care dollar, pharmaceutical expenditures have come under considerable scrutiny largely due to a double-digit rate in cost growth in recent years. This growth rate in the pharmaceutical sector has far surpassed other medical care cost components such as hospitalizations and physician salaries. Published studies suggest that increasing rates of utilization of old and new drugs, not rising drug prices, is the main driving force behind increases in drug spending. It follows that health care payers, in an attempt to address the rapid escalation in pharmaceutical costs, will intensely examine the “value” of new drugs to determine if the additional dollars spent are justified in terms of incremental health benefits.

The availability of the cyclooxygenase-2 (COX-2)—selective inhibitors (coxibs) has markedly changed the management of arthritis. Health care payers have closely followed the widespread adoption of coxibs and resultant increases in pharmaceutical expenditures for this disease and related conditions. Determining which nonsteroidal anti-inflammatory drug (NSAID) users should have access to these more expensive agents should depend on the clinical and economic effects of these agents. In order to constrain health care expenditures, clinical practice guidelines and drug formularies often recommend using less expensive (often generically available compounds) NSAIDs first while restricting coxibs for treatment failures. Since chronic NSAID users may fail initial therapy, experience dyspepsia, or suffer a complication necessitating a change in therapy, the clinical and cost consequences of NSAID therapy depend on subsequent diagnostic and treatment decisions that occur over the entire natural history of disease. Thus, the most cost-effective NSAID regimen does not depend entirely on the differences in complication rates and/or treatment costs at time of use, but also on the likelihood of switching medications, the variation in patients’ symptomatic response, and the resultant ulcer- and non-ulcer–related health care expenditures.

NSAID THERAPY AND ASSOCIATED GASTROPATHY

Nonselective NSAIDs are a mainstay of medical treatment for arthritis, owing to their well-established anti-inflammatory and analgesic effects. These NSAIDs account for more than 70 million annual prescriptions, and more than 30 billion over-the-counter tablets are sold every year in the United States. NSAIDs are associated with adverse gastrointestinal (GI) effects ranging from mild dyspepsia to serious, potentially fatal complications such as bleeding peptic ulcer. Although the probability is low that any chronic NSAID user will experience a drug-related complication, the fact that millions of Americans use these agents on a regular basis makes nonselective NSAID-related gastropathy an important problem from both clinical and economic perspectives.

The Arthritis, Rheumatism, and Aging Medical Information System (ARAMIS), a prospective observational database of 36,000 rheumatoid arthritis patients, reported that 1.3 serious GI complications occurred for every 100 patient-years of NSAID use. Based on these data, an estimated 100,000 hospitalizations and 10,000 to 20,000 deaths each year in the United States can be attributed to complications related to prescription NSAIDs. The risk of a hospitalization caused by a GI adverse event is even more pronounced among elderly NSAID users; these agents should be used with caution in this patient subgroup.

The high costs that result from NSAID-related GI toxicity have been noted for many years. Studies using claims databases have reported that nearly one-third of aggregate medical expenditures for arthritis patients can be attributed to GI adverse effects.
Among elderly members of one health maintenance organization, Johnson and colleagues estimated that for every dollar spent on NSAID therapy, $0.35 was spent to treat NSAID-related gastropathy.11 The scope of this problem has led the Food and Drug Administration (FDA) to include a formal warning in the package labeling regarding the risk of adverse GI events for patients using traditional NSAIDs.12 Despite attempts to educate patients, most regular NSAID users have a lack of awareness of the potential side effects of NSAIDs.13 Controversy remains among clinicians on how best to weigh the potential clinical benefits of nonselective NSAIDs against the possibility of adverse events associated with their use. Identification of risk factors for the development of NSAID-related complications may aid clinicians in identifying patients at highest risk.14

There is no consensus on how best to minimize NSAID-related adverse events, but it is clear that assessments of available treatment options must account for both clinical effects and economic consequences. Strategies to prevent NSAID-related gastropathy include discontinuing the NSAID or decreasing its dosage, or using a non-NSAID analgesic, gastroprotective agent (GPA), or a safer NSAID with similar efficacy (Table 1).

GPAs are often used to prevent the GI adverse effects of nonselective NSAID therapy. GPAs, however, are not completely effective in prophylaxis and treatment of NSAID-related GI events, may have their own side effects, and contribute substantially to the costs of treatment. Coprescribing rates of GPAs in the setting of nonselective NSAID use range from 17% to 34%.15 These agents include misoprostol, histamine2-receptor antagonists, and proton pump inhibitors.

Misoprostol is approved by the FDA for use to prevent NSAID-related adverse events. Published economic analyses suggest that this agent is cost-effective for patients at increased risk for NSAID gastropathy.15 However, misoprostol is associated with its own adverse effects.16 As a result, acid inhibitory drugs are more frequently utilized to reduce NSAID-associated symptoms and adverse effects. While histamine2-receptor antagonists may reduce NSAID-associated dyspepsia,17 these agents are not effective in preventing NSAID-associated ulcers and their related complications at traditional dosages.18 Since potent acid suppression with high-dose histamine2 antagonists19 or proton pump inhibitors20–22 has been demonstrated to heal and even prevent the recurrence of endoscopic ulcers in randomized controlled trials, these agents have become common management options.

### PHARMACOECONOMICS OF COXIB THERAPY

Generic NSAIDs are a cost-effective way to treat arthritis pain. However, the cost of treating NSAID-related gastropathy adds to cost of using NSAIDs. Use of GI co-therapies and endoscopy rates decrease with use of COX-2 inhibitors.

COX-2–selective inhibitors are cost-effective in patients at increased risk for developing GI-related side effects.

Any patient with a history of prior GI bleeding or any patient with rheumatoid arthritis who is steroid dependent should be prescribed a COX-2–selective inhibitor first line instead of a traditional NSAID.

There is an incremental cost to using a COX-2–selective inhibitor versus a generic NSAID. This cost differential is nominal in high-risk patients but becomes more pronounced in low-risk patients.

### CLINICAL AND ECONOMIC RATIONALE FOR COX-2–SELECTIVE INHIBITORS

An attractive alternative to GPAs to reduce NSAID toxicity is the use of a COX-2–selective inhibitor, an equally effective anti-inflammatory agent with reduced propensity for GI injury. The differences in the relative safety of currently available NSAIDs may be explained by their pharmacologic properties, as discussed elsewhere in this supplement in greater detail. The elucidation of the roles of the cyclooxygenase isoenzymes (COX-1 and -2) has led to an improved understanding of the pathophysiolo-

### TABLE 1

<table>
<thead>
<tr>
<th>Strategies to prevent NSAID-related gastropathy</th>
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<tr>
<td>Stop the NSAID</td>
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<tr>
<td>Decrease the NSAID dosage</td>
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<tr>
<td>Use a safer NSAID with similar efficacy</td>
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<tr>
<td>Coprescribe a gastroprotective agent</td>
</tr>
<tr>
<td>Misoprostol</td>
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<tr>
<td>Histamine2-receptor antagonist</td>
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<tr>
<td>Proton pump inhibitor</td>
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<tr>
<td>Use a non-NSAID analgesic</td>
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**ECONOMIC RATIONALE**

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gy of NSAID gastropathy.23 (See articles by Bingham and by Cronstein, this supplement). The relative inhibition of COX-1 activity (central to the maintenance of GI mucosal integrity) to COX-2 activity (reduces inflammation) may provide an explanation for the basis and observed rates of different NSAIDs to produce varying rates of GI injury.8 The capacity of NSAIDs to inhibit platelet function (by inhibition of COX-1) may also influence whether an NSAID-associated lesion remains silent or develops clinically apparent bleeding.

The scientific evidence that coxibs provide superior GI safety when compared with nonselective NSAIDs has emerged from the laboratory and from clinical studies. The steps necessary to prove the “coxib hypothesis,” from test tube to human subjects, are shown in Figure 1. Laboratory-based investigations demonstrating differences in COX-1 and COX-2 selectivity among available NSAIDs and their impact on prostaglandin synthesis in tissue culture are discussed elsewhere in this supplement. Translating such findings from the laboratory bench to bedside is often complicated, but a notable example of this was a single study that demonstrated significantly less fecal red-blood-cell loss by healthy subjects taking rofecoxib when compared with healthy individuals given similar doses of ibuprofen.24 The controlled clinical studies in arthritis patients, which found that patients taking coxibs experienced significantly fewer endoscopic lesions and clinically meaningful GI events, are described in detail in the supplement article by James Scheiman, MD.25

**NSAID CHOICE AND HEALTH CARE RESOURCE USE**

To accurately assess the clinical and economic trade-offs between a lower rate of drug-related complications and resultant higher pharmaceutical expenditures, both the incremental costs and benefits should be carefully measured and compared with available alternatives. On the cost side, it is critical to look beyond direct cost comparisons of drugs under investigation. All the health care resources incurred over the entire episode of care must be accounted for, especially since a proportion of individuals prescribed one agent may eventually be prescribed the other. The clinical indications for, and side effects of, chronic anti-inflammatory therapy often necessitate changing NSAIDs or adding cotherapy for prophylaxis or symptom control.

Analysis of data from the prospective outcome trials described by Dr Scheiman in this supplement provides a perspective on resource utilization that can be used to make an economic argument for the use of COX-2-selective inhibitors in certain populations. Using data from the Vioxx Gastrointestinal Outcomes Research (VIGOR) trial,26 Bombardier and colleagues compared rates of use of GPAs (histamine2-receptor antagonists, proton pump inhibitors, sucralfate, and prostaglandins) and GI diagnostic procedures and hospitalizations for upper GI perforation, ulcer, or bleeding in patients treated with either rofecoxib or naproxen. The rofecoxib-treated patients were significantly less likely to require new use of GPAs (11.2% versus 14.5%, \(P < .001\)) and were hospitalized significantly less often for perforation, ulcer, or bleeding (.4% versus .9%, \(P = .01\); Table 2).27

Similar decreases in resource use were found in an analysis of the subset of participants reporting GI adverse events (Table 2). New use of GPAs was significantly less in the rofecoxib group (25.5% versus 32.2%, \(P < .001\)). Rofecoxib-treated patients also had fewer GI procedures (12.4% versus 15.8%, \(P = .01\)) and fewer hospitalizations for GI perforation, ulcer, or bleeding (1.2% versus 2.3%, \(P = .02\)).27

An analysis of resource utilization using pooled data from rofecoxib trials in patients with osteoarthritis was recently reported. Under base-case circumstances, cost savings attributable to fewer GI adverse events with rofecoxib (versus nonselective

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**Figure 1. Proving the “coxib hypothesis.”**
**TABLE 2**

Rates of GI events, new use of GPAs, and GI procedures in rofecoxib versus naproxen\(^\text{27}\)

<table>
<thead>
<tr>
<th></th>
<th>Rofecoxib</th>
<th>Naproxen</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VIGOR</strong> ((n = 8,076))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalizations for PUBs</td>
<td>0.4%</td>
<td>0.9%</td>
<td>= .01</td>
</tr>
<tr>
<td>New GPAs</td>
<td>11.2%</td>
<td>14.5%</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>GI procedures</td>
<td>5.6%</td>
<td>6.9%</td>
<td>= .02</td>
</tr>
<tr>
<td><strong>VIGOR subset</strong> ((n = 2,937))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalizations for PUBs</td>
<td>1.2%</td>
<td>2.3%</td>
<td>= .02</td>
</tr>
<tr>
<td>New GPAs</td>
<td>25.5%</td>
<td>32.2%</td>
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<td>12.4%</td>
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<td>= .01</td>
</tr>
</tbody>
</table>

PUBs = perforation, ulcer, or bleeding; GI = gastrointestinal; GPAs = gastroprotective agents.
Using the best data available, it appears that for patients at average risk for developing GI-related complications, the unrestricted use of COX-2–selective inhibitors could decrease ulcer-related adverse events but at an incremental cost. For high-risk patients, unrestricted access to COX-2–selective inhibitors could be both clinically and economically advantageous because of the high likelihood of adverse events and the safety benefits of coxibs. Therefore, even in an era of cost constraint, COX-2–selective inhibitors should be offered as first-line agents to these high-risk patients.

REFERENCES